IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant:	Tavares et al.	Application No.:	10/045,607
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Examiner:	Isis A. D. Ghali	Attorney Docket:	208.1004US
Art Unit:	1611	Customer No.:	23280
Title:	**LORATADINE TRANSDERMAL DEVICE AND METHODS**		

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

November 17, 2010

APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Sir:

Appellants submit this brief for the consideration of the Board of Patent Appeals and Interferences (the "Board") in support of their appeal of the Final Rejection dated January 5, 2010, in this application. The balance of the statutory fee of $ 40.00 for filing an appeal brief is being paid concurrently herewith, as $ 500.00 for filing an appeal brief was paid on January 25, 2006. If any additional fees are deemed to be due at this time or any fees have been overpaid, the Commissioner is authorized to charge the payment of the additional fees or credit the overpayment to Deposit Account No. 50-0552.

I. REAL PARTY IN INTEREST

The real party in interest is Purdue Pharma L.P., a Delaware limited partnership having offices at One Stamford Forum, Stamford, CT 06901, and the assignee of the entire right, title and interest in the above-identified patent application. The invention was assigned to Purdue Pharma L.P. from Euro-Celtique S.A. by an assignment which was recorded on January 27, 2006, at reel 017489, frame 0213. The invention was assigned to Euro-Celtique S.A. from the inventors, Lino Tavares, Ihor Shevchuk, Mark Alfonso, Geraldine Marcenyac, and Kirti H. Valia, by an assignment which was recorded on May 15, 2002, at reel 012895, frame 0736.

II. RELATED APPEALS AND INTERFERENCES

Appellants, their legal representatives, and assignee are not aware of any appeal, interference or judicial proceeding that directly affects, will be directly affected by, or will have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

Claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 are pending and have been finally rejected by the Examiner as per the Final Office Action mailed on January 5, 2010.

The rejection of claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 is thus appealed. A copy of claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 is attached hereto as Appendix A.

IV. STATUS OF AMENDMENTS

Claim 20 was amended to correct a typographical error after rejection of claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 in the Final Office Action mailed on January 5, 2010. The Advisory Action mailed on May 27, 2010, indicates that the amendment was entered. A Notice of Appeal was filed on May 18, 2010, and received by the U.S.P.T.O. on May 18, 2010.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Independent claim 8 recites a method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient (e.g., page 5, 2nd paragraph), comprising

administering loratadine transdermally to the human patient by applying a transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a softening agent; and (iv) a solvent (e.g., page 11, 4th full paragraph), to the skin of a patient (e.g., page 5, 2nd paragraph), and

maintaining said transdermal delivery system in contact with the skin of the patient for at least 5 days (e.g., page 5, 2nd paragraph),

said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval (e.g., page 5, 2nd paragraph), and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval (e.g., page 5, 2nd paragraph),

said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml (e.g., page 6, 1st paragraph);

said transdermal delivery system having a mean relative release rate of from about 2.8 $\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours (e.g., page 9, 5th paragraph);

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours (e.g., page 9, 5th paragraph);

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system

surface area at 72 hours (e.g., page 9, 5th paragraph);

and a mean relative release rate of from about 1.8 μg/cm^2/hr to about 9.9 μg/cm^2/hr of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water (e.g., page 9, 5th paragraph).

Dependent claim 9 recites the method of claim 8 wherein the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours (e.g., page 7, 1st paragraph).

Dependent claim 10 recites the method of claim 8, further comprising maintaining an effective mean relative release rate of said transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval (e.g., page 7, 2nd paragraph); and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval (e.g., page 7, 2nd paragraph).

Dependent claim 11 recites the method of claim 8, further comprising providing a mean relative release rate of loratadine from said transdermal delivery system to provide a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours after application of said transdermal delivery system onto the skin of the patient (e.g., page 5, last paragraph).

Dependent claim 13 recites the method of claim 8, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system (e.g., page 6, 2nd paragraph).

Independent claim 20 recites a transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a softening agent; and (iv) a solvent (e.g., page 7, 6th full paragraph),

the transdermal delivery system provides a mean relative release rate of from about 2.8

$\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours (e.g., page 9, 5th paragraph);

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours (e.g., page 9, 5th paragraph);

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 72 hours (e.g., page 9, 5th paragraph); and

from about 1.8 $\mu g/cm^2/hr$ to about 9.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell having a receptor chamber containing a 40:60 mixture of ethanol:water (e.g., page 9, 5th paragraph);

said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within 36 hours from the initiation of the dosing interval (e.g., page 5, 1st paragraph), and a plasma level of loratadine of at least about 0.1 ng/ml by about 6 hours after application of said transdermal delivery system onto the skin of a human patient (e.g., page 5, last paragraph); said transdermal delivery system maintaining a therapeutic blood level until the end of at least a five-day dosing interval (e.g., page 5, second paragraph) and

a plasma level of loratadine at steady state of about 3 ng/ml (e.g., page 6, 1st paragraph).

Dependent claim 29 recites the transdermal delivery system of claim 20, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system (e.g., page 6, second paragraph).

Independent claim 46 recites a method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient (e.g., page 5, 2nd paragraph), comprising

administering loratadine transdermally to the human patient by applying a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof to the skin of a patient (e.g., page 5, 2nd paragraph), and

maintaining said transdermal delivery system in contact with the skin of the patient for at

least 5 days (e.g., page 5, 2nd paragraph),

said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval (e.g., page 5, 2nd paragraph), and

thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval (e.g., page 5, 2nd paragraph),

said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml (e.g., page 6, 1st paragraph);

said transdermal delivery device comprising a backing layer which is substantially impermeable to the loratadine or pharmaceutically acceptable salt thereof (e.g., page 11, 4th full paragraph); and a reservoir layer consisting essentially of 20 to 90% by weight of a polymeric matrix (e.g., page 11, 4th full paragraph), 0.1 to 30% by weight of a softening agent (e.g., page 11, 4th full paragraph); 0.1 to 20% by weight of loratadine base or of a pharmaceutically acceptable salt thereof (e.g., page 11, 4th full paragraph) and 0.1 to 30% (e.g., page 11, 4th full paragraph) by weight of a solvent, for the loratadine or salt thereof;

said transdermal delivery system having a mean relative release rate of from about 2.8 $\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours (e.g., page 9, 5th paragraph);

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours (e.g., page 9, 5th paragraph);

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 72 hours (e.g., page 9, 5th paragraph);

and a mean relative release rate of from about 1.8 $\mu g/cm^2/hr$ to about 9.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water (e.g., page 9, 5th paragraph).

Dependent claim 50 recites the method of claim 8, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the

group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate (e.g., page 19, 3rd and 4th full paragraphs).

Dependent claim 51 recites the transdermal delivery system of claim 20, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate (e.g., page 19, 3rd and 4th full paragraphs).

Dependent claim 52 recites the method of claim 46, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate (e.g., page 19, 3rd and 4th full paragraphs).

Dependent claim 53 recites the method of claim 8, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof (e.g., page 22, 1st full paragraph).

Dependent claim 54 recites the transdermal delivery system of claim 20, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof (e.g., page 22, 1st full paragraph).

Dependent claim 55 recites the method of claim 46, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof (e.g., page 22, 1st full paragraph).

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 are patentable under U.S.C. § 103(a) over the combination of U.S. Patent No. 4,910,205 to Kogan et al. ("the Kogan reference"), paragraph [0123] of the present specification and U.S. Patent No. 5,968,547 to Reder et al. ("the Reder reference").

VII. ARGUMENTS

Rejection of claims 8-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 under U.S.C. § 103(a) over the combination of the Kogan reference, paragraph [0123] of the present specification and the Reder reference should be reversed, because a *prima facie* case of obviousness has not been established, and because Appellants have shown that elements of the present claims are not taught by or expected from the disclosure of the cited references.

A. A PRIMA FACIE CASE OF OBVIOUSNESS HAS NOT BEEN ESTABLISHED

Appellants respectfully submit that a *prima facie* case of obviousness has not been established because (i) the claimed invention is being used as an instruction manual or template to piece together teachings of prior art so that the claimed invention is rendered obvious and unpatentable; moreover, the rejection is based on something that is not prior art to the present application; and (ii) elements of the present claims are not taught by or expected from the cited references.

The MPEP makes clear that the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP, Section 2142. "If, however the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness." MPEP, Section 2142. The Board of Patent Appeals and Interferences holds the view that:

> … obviousness cannot be proven merely by showing that the elements of a claimed device were known in a prior art; it must be shown that those of ordinary skill in the art would have had some "apparent reason to combine the known elements in the fashion claimed …
> [Similarly,] obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that result in the claimed composition.

Appeal No. 2007-4423, Decision of Appeal dated July 23, 2008.

Appellants respectfully submit that the Examiner has not carried his burden in the present

case.

1. The claimed invention is being used as an instruction manual or template to piece together teachings of prior art so that the claimed invention is rendered obvious and unpatentable, and the rejection is based on something that is not prior art to the present application

Appellants respectfully submit that there is no connection between the Kogan reference and the Reder reference in the absence of the present specification, and that the present specification is being used as an instruction manual or template to piece together teachings of the cited references.

"It is impermissible to use the claimed invention as an instruction manual or 'template' to piece together teachings of prior art so that the claimed invention is rendered obvious and unpatentable." *In re John R. Fritch*, 972 F.2d 1260 (Fed. Cir. 1992). "To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction—an illogical and inappropriate process by which to determine patentability." *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1983) (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983)). "The invention must be viewed not after the blueprint has been drawn by the inventor, but as it would have been perceived in the state of the art that existed at the time the invention was made." *Id.* (citing *Interconnect Planning Corp. v. Feil,* 774 F.2d 1132, 1138 (Fed. Cir. 1985)).

Independent claims 8, 20 and 46 all recite in part a transdermal delivery system of loratadine which maintains "a plasma level of loratadine at steady state of about 3 ng/ml" and provides the in-vitro release profiles of loratadine recited in the claims.

The combination of the cited references does not disclose any plasma levels of loratadine and does not teach controlling a steady state plasma level of loratadine by adjusting/controlling the rate of release of loratadine at 24 hours, 48 hours, 72 hours and 96 hours.

The Examiner does not point out what in the cited references connects the loratadine

described in the Kogan reference to the specific compositions and the release rates described in the Reder reference, and the Appellants are not able to find such a connection in the cited references.

Rather than relying on the information in the cited references, the Examiner purports that the connection between loratadine described in the Kogan reference to the specific compositions and the release rates described in the Reder reference can be found in paragraph [0123] of the present specification. The Examiner contends that there is an admission in paragraph [0123] that something in paragraph [0123] is "prior art" to the Appellants. *See* Advisory Action mailed on May 27, 2010, page 2.

Appellants respectfully submit that paragraph [0123] of the present specification does not contain such an admission.

The Manual of Patent Examining Procedure, section 2129 [R-6], states:

> A statement by an applicant > in the specification or made< during prosecution identifying the work of another as "prior art" is an admission ... which can be relied upon for both anticipation and obviousness determinations, regardless of whether the admitted prior art would otherwise qualify as prior art under the statutory categories of 35 U.S.C. § 102.

(emphasis in the original).

Appellants respectfully submit that paragraph [0123] does not identify anything as "prior art" to the Appellants. Paragraph [0123] is listed in the Detailed Description section of the present specification and recites:

> The adult oral dosage for loratadine is 10 mg/day. The bioavailability for the drug is 20%, expressed as fraction, 0.20 of the oral dose made available to the blood stream from gastrointestinal absorption. A release rate for a loratadine transdermal delivery system was calculated from this data. 0.20 of the oral 10 mg daily dose provides 2.0 mg of loratadine available into the blood stream. Therefore, an equal dose is required to be delivered transdermally. 2.0 mg/day is converted to 2000 mcg/24 hours. This would require delivery of 83.3 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 83.3 mcg/hour/40 cm^2 by 40, yields a release rate of 2.1 mcg/hour/cm^2 of transdermal patch surface area. To account for drug elimination, further

> pharmacokinetic data and physiological data was required. The plasma concentration at steady state for loratadine is 0.002 mcg/ml. The physiological clearance rate is 196,000 ml/hour. The dosing rate is obtained from the product of the steady state concentration of loratadine and a representative clearance rate. This product is 392 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 392 mcg/hour/40 cm^2 by 40, yields a release rate of 9.8 mcg/hour/cm^2 of transdermal patch surface area. One of skill would expect a larger input rate or flux to maintain a steady state concentration in consideration of the loss of drug in the plasma due to elimination. A confirmatory calculation for flux requires further pharmacokinetic parameters. The volume of distribution for loratadine is 1,660,000 ml and the half-life is 8.4 hours. The elimination rate constant is 0.693/half-life. The product of steady state concentration, volume of distribution and elimination rate constant yields a rate of 274 mcg/hour. The largest desirable surface area for a transdermal patch is about 40 cm^2. Dividing 274 mcg/hour/40 cm^2 by 40, yields a release rate of 6.85 mcg/hour/cm^2 of transdermal patch surface area.

Accordingly, there is nothing in paragraph [0123] that qualifies as an admission that something is "prior art" to the Appellants, because paragraph [0123] does not identify anything as "prior art" to the Appellants.

Appellants respectfully note that paragraph [0123] was amended during prosecution. The first sentence of the original paragraph [0123] recited "[t]he pharmacokinetic information for loratadine is available in the literature," and was deleted from paragraph [0123] during prosecution. Appellants respectfully submit that this sentence also did not identify the work of another as "prior art," and therefore did not qualify as an admission.

Appellants further note that the cited references do not show how to calculate the claimed mean relative release rates of loratadine from the data regarding the bioavailabity of loratadine.

The Examiner acknowledges on page 5 of the final Office Action mailed on January 5, 2010, that the Kogan reference "does not teach the specific delivery profile of loratadine, the specific amounts of different ingredients, or specific structure and formulation of a transdermal delivery device including specific polymer, specific solvents and specific softening agents in the transdermal delivery system." Nevertheless, the Examiner takes the position, purely on the knowledge learned from the present specification, that a skilled person would have altered the

formulation of the Kogan reference to an entirely different formulation (i.e., the buprenorphine formulation of Reder), and arrived at the presently claimed plasma concentration of loratadine at steady state and the claimed release profiles. The Examiner asserts that the claimed formulation of a transdermal device including specific polymer, specific solvents and specific softening agents is described in the Reder reference, because the **present** specification states on page 24, first full paragraph, that "[a]ny type of transdermal delivery system may be used in accordance with the methods of present invention as long as the desired pharmacokinetic and pharmacodynamic response[s] are attained."

The assertion however ignores the fact that there is no mention of the "desired" pharmacokinetic parameters of loratadine (i.e., steady state plasma concentration) in the Reder patent, or that the Reder reference is not in the field of Appellants' endeavor and is not reasonably pertinent to the particular problem with which the Appellants were concerned- "[a] method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient" or administration of loratadine as recited in the present claims. The Reder reference is directed to the treatment of pain, e.g., by applying buprenorphine transdermally. *See e.g.* Abstract.

This assertion further ignores the fact that there is simply no information provided in the cited references that provides any indication that loratadine may be incorporated into the transdermal delivery devices of the Reder reference or may provide the claimed steady state plasma concentration of loratadine and release profile of loratadine.

The assertion also ignores the fact that there is nothing in the cited references that suggests maintaining the plasma level of loratadine at steady state of about 3 ng/ml by adjusting/controlling the rate of release of loratadine at 24 hours, 48 hours, 72 hours and 96 hours.

Finally, the assertion is based on the disclosure of the present specification, which is not "prior art" to the present application.

For the foregoing reasons, Appellants submit that the rejection is deficient and improper on its face and should be reversed.

2. The elements of the present claims are not expected from the cited references

Appellants submit that that the elements of the present claims are not expected from the cited references.

a. Claims 8, 9, 10, 11, 13, 14, 16, and 53

Independent claim 8 is directed in part to a **method** of treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient comprising a step of "maintaining a plasma level of loratadine at steady state of about 3 ng/ml" by administering loratadine transdermally to the human patient via a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof, the system exhibiting the claimed release profile (specific release rates at 24 hours, 48 hours, 72 hours, and 96 hours).

(i) "A plasma level of loratadine at steady state of about 3 ng/ml" is not taught or expected from the cited references

Appellants respectfully submit that the step of "maintaining a plasma level of loratadine at steady state of about 3 ng/ml" is not expected from the cited references.

It was held that references which do not teach the specific pharmacokinetic parameters do not render these pharmacokinetic parameters obvious. Specifically, the court stated that "just as the absence of the PK [pharmacokinetic] limitations … was sufficient … to defeat an anticipation claim; **it is also sufficient here to defeat … obviousness challenge**". See *Abbott Laboratories v. Sandoz, Inc.*, 2007 WL 4287501 at 28 (N.D.Ill 2007) (emphasis added).

The Examiner states on page 4 of the Office Action that "[t]he claimed plasma level of

loratadine of the prior [art] is ... expected to be the same as those disclosed by the prior art since the prior art teaches the same **daily dose** and hourly release rate of loratadine for the same period of time as instantly claimed."

The daily dose of loratadine however is not recited in instant claim 8, and, as established in section B below, the steady state plasma concentration of loratadine calculated from the data in the Kogan reference is different and unexpected from the steady state concentration of loratadine recited in claim 8. Section B below establishes that the steady state concentration of loratadine recited in the present claims (3 ng/ml) is 4.3 times higher or 6.3 times higher than the calculated 0.69 ng/ml and 0.48 ng/ml steady state loratadine concentrations of the Kogan reference. Appellants respectfully submit that the skilled person would understand that "about 3 ng/ml" recited in claim 8 does not encompass values that are 4.3 times lower or 6.3 times lower than 3 ng/ml.

Appellants further submit that the cited references also do not show how to calculate the claimed mean relative release rates of loratadine from the data regarding the bioavailabity of loratadine.

Appellants also submit that the presently claimed plasma levels of loratadine at steady state and release profiles cannot be a result of purported optimization of the formulations of the cited references. As acknowledged by the Examiner on page 3 of the Advisory Action, "[a] particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation."

The cited references do not recognize that the loratadine steady state plasma concentration can be adjusted/controlled by adjusting/controlling the rate of release of loratadine at 24 hours, 48 hours, 72 hours and 96 hours; and therefore the presently claimed plasma levels of loratadine at steady state and release profiles cannot be a result of purported optimization of the formulations of the cited references. Appellants respectfully submit that the disclosure in

column 3, lines 56-60, of the Kogan reference that "the particular dosage described [therein] ... may be varied depending on the size and age of the patient and may also depend on the conditions" refers to the daily dosage of loratadine (mg of loratadine), and does not teach or suggest adjusting loratadine's steady state plasma concentration by adjusting/controlling the rate of release of loratadine at 24 hours, 48 hours, 72 hours and 96 hours from the transdermal delivery system.

Further, as acknowledged by the Examiner on page 5 of the Office Action, the Kogan reference "does not teach the specific structure and formulation" of the presently claimed system. The Reder reference also does not teach or suggest the presently claimed system, because it does not disclose loratadine. The combination of the Kogan reference and the Reder reference does not therefore teach or suggest the claimed system. It is therefore cannot be expected that a system suggested by the combination of the cited references will produce the present claimed steady state plasma concentration of loratadine. In fact, as stated above, the steady state concentration of loratadine recited in the present claims is 4.3 times higher or 6.3 times higher than the calculated 0.69 ng/ml and 0.48 ng/ml steady state loratadine concentrations of the Kogan reference, and "about 3 ng/ml" recited in claim 8 does not encompass values that are 4.3 times lower or 6.3 times lower than 3 ng/ml.

Accordingly, Appellants submit that the steady state plasma concentration of loratadine recited in claim 8 is not taught by or expected from the cited references.

ii. The step of maintaining the claimed release profile of loratadine is not taught or suggested by the cited references.

The cited references also do not teach or suggest the claimed release profile (specific release rates at 24 hours, 48, hours, 72 hours, and 96 hours) as recited in claim 8.

The Examiner purports to support the rejection by making a conclusory statement on page 2 of the Advisory Action —"the present claims as a whole is taught by the combination of the cited references, therefore, prima facie case of obviousness has been established."

However, "rejections on obviousness cannot be sustained with mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness," *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006).

Appellants respectfully submit that the combination of the cited references does not teach or suggest the method recited in claim 8. The Examiner acknowledges on page 5 of the Office Action that the Kogan reference "does not teach the specific delivery profile of loratadine."

Appellants respectfully submit that this deficiency is not cured by the Reder reference, because (i) loratadine, an antihistamine, is not a functional, pharmacological or structural equivalent of buprenorphine, an opioid, and (ii) the Reder reference does not disclose loratadine or suggest that loratadine may be included in its formulations. Appellants respectfully submit that, to the extent that the Reder reference teaches relative mean release rates, given the vast physical, chemical and pharmacological differences buprenorphine and loratadine, the skilled person would not have extended the release rates of buprenorphine disclosed in the Reder reference to the release rates of loratadine recited in instant claim 8.

Appellants respectfully reiterate that there is no information in the cited references that provides any indication that loratadine may be incorporated into the transdermal delivery devices of the Reder reference and provide the claimed release profile (specific release rates at 24 hours, 48, hours, 72 hours, and 96 hours) of loratadine as recited in claim 8. Further, there is no information in the cited references that speaks of the unacceptability of the Kogan release rates or suggests that the rate recited in the present claims may be efficacious or beneficial.

Appellants thus submit that the cited references do not provide a reason for the skilled person to modify the formulation of the Kogan reference to provide the release rates of the Reder reference. Appellants respectfully reiterate that the cited references do not recognize that the loratadine steady state plasma concentration can be adjusted/controlled by adjusting/controlling

the rate of release of loratadine at 24 hours, 48 hours, 72 hours and 96 hours, and do not disclose substantially the same formulation as recited in claim 8; therefore, the presently claimed release profiles cannot be a result of purported optimization of the formulations of the cited references.

In response to the Examiner's statement on page 3 of the Advisory Action that "Kogan teaches mean average release rate from 1.4 $\mu g/cm^2/hr$ to 14 $\mu g/cm^2/hr$ [in Table I] and applicant[s] claim mean average release rate from 1.8 $\mu g/cm^2/hr$ to 9.9 $\mu g/cm^2/hr$," Appellants respectfully submit that the flux rates in Table I of the Kogan reference are "at approximate **steady state**," rather than at " 24 hours; ... 48 hours; ... 72 hours; and ... 96 hours" as recited in independent claim 8. Appellants therefore submit that the Examiner's comparison is inappropriate.

Accordingly, Appellants submit that the release profile of loratadine (specific release rates at 24 hours, 48, hours, 72 hours, and 96 hours) as recited in present claim 8 is not taught or suggested by the cited references.

iii. The <u>combination</u> of the claimed steady state plasma level of loratadine and release profile is not suggested by the cited references

As stated above, the cited references do <u>not</u> disclose the connection between the claimed steady state plasma level of loratadine and release profile. Accordingly, the combination of the cited references cannot teach or suggest the desirability of the combination of these parameters or provide a reason for the skilled person to formulate and administer loratadine transdermally such that the combination of the claimed steady state plasma level of loratadine and release profile is attained.

For the foregoing reasons, Appellants submit that a *prima facie* case of obviousness of claim 8 has not been established, and that claim 8 is not taught by or expected from the cited references.

Claims 9, 10, 11, 13, 14, 16, and 53 depend from claim 8, and therefore incorporate features of claim 8 which are not taught or suggested by the combination of the cited references. Accordingly, a *prima facie* case of obviousness of claims 9, 10, 11, 13, 14, 16, and 53 has not been established as well.

(b) Claim 9 (argued separately)

Claim 9 is directed to a method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, such that "the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours."

The Examiner has not pointed out the portions of the cited references which disclose a step of administering loratadine transdermally such that "the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours release," nor can Appellants find such a disclosure in the cited references.

Appellants respectfully submit that loratadine is not a functional, pharmacological or structural equivalent of buprenorphine, and therefore the steps of maintaining the plasma levels of **buprenorphine** such that they do not decrease by more than 30 % over 72 hours as described in the Reder reference do not read on the step of administering loratadine transdermally such that "the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours release" as recited in the instant claim 9.

Appellants therefore submit that a *prima facie* case of obviousness of claim 9 has not been established, and that claim 9 is not taught or suggested by the combination of the cited references.

(c) Claim 10 (argued separately)

Claim 10 recites in part a step of "maintaining an effective mean relative release rate of

said transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval."

The Examiner has not pointed out the portions of the cited references which describe such a step, nor were the Appellants able to find such a step in the cited references.

Appellants respectfully reiterate that loratadine is not a functional, pharmacological or structural equivalent of buprenorphine, and therefore the steps of maintaining **buprenorphine** mean relative release rates as described in the Reder reference do not read on the step of maintaining **loratadine** mean relative release rates as recited in claim 10.

Appellants therefore submit that a *prima facie* case of obviousness of claim 10 has not been established, and that claim 10 is not taught or suggested by the combination of the cited references.

(d) Claim 11 (argued separately)

Claim 11 recites in part a step of "maintaining an effective mean relative release rate of said transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval."

The Examiner has not pointed out the portions of the cited references which describe such a step, nor were the Appellants able to find such a step in the cited references.

Appellants therefore submit that a *prima facie* case of obviousness of claim 11 has not been established, and that claim 11 is not taught or suggested by the combination of the cited references.

(e) Claim 13 (argued separately)

Claim 13 recites a step of maintaining a plasma level of loratadine "from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval" of transdermal delivery system.

The Examiner has not pointed out the portions of the cited references which describe such a step, nor were the Appellants able to find such a step in the cited references. In fact, the cited references do not disclose any plasma levels of loratadine.

Appellants therefore submit that a *prima facie* case of obviousness of claim 13 has not been established, and that claim 13 is not taught or suggested by the combination of the cited references.

(f) Claim 50 (argued separately)

Claim 50 is directed to a method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, transdermally, wherein the transdermal delivery system comprises loratadine and a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

The Examiner has not pointed out the portions of the cited references which would have suggested combining loratadine with (i) a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and (ii) a solvent selected from the group consisting of a

monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate" as recited in claim 50. Appellants were also not able to find such a suggestion in the cited references.

Appellants therefore submit that a *prima facie* case of obviousness of claim 50 has not been established, and that claim 50 is not taught or suggested by the combination of the cited references.

(g) Claim 53 (argued separately)

Claim 53 is directed in part to a method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, transdermally, wherein the transdermal delivery system comprises "a solution of an active agent consisting of loratadine" as recited in claim 53.

Appellants submit that the combination of the cited references does not teach or suggest a transdermal delivery system comprising "a solution of an active agent consisting of loratadine" as recited in claim 53, because the cited references do not teach or suggest a solution of loratadine. Appellants respectfully note that the test for measuring the flux rates used in the Kogan reference is unsuitable for solution formulations. The Kogan reference describes measuring flux rates with a Franz diffusion cell method. *Column 3, lines 28-30.* According to Development of a Dynamic Skin Permeation System for Long-Term Permeation Studies[1], the Franz diffusion cell test is "**not** suitable for evaluation of solution or suspension-formulations ... due to its inherent upright, open donor compartments design, which does not permit the use of any stirring setup as in the receptor compartment." A copy of the Development of a Dynamic Skin Permeation System for Long-Term Permeation Studies was submitted as reference AM in the Information Disclosure Statement filed on July 28, 2008. Accordingly, Appellants respectfully submit that the Kogan reference does not teach or suggest a transdermal delivery system comprising a solution of loratadine.

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1 Development of a Dynamic Skin Permeation System for Long-Term Permeation Studies, Drug development and Industrial Pharmacy, 10(4), page 577 (1984).

The Reder reference cannot cure this deficiency of the Kogan reference, because there is no mention of loratadine in the Reder reference.

Accordingly, the combination of the cited references would not have suggested to one skilled in the art a transdermal delivery system comprising a solution of loratadine as recited in claim 53.

Appellants therefore submit that a *prima facie* case of obviousness of claim 53 has not been established, and that claim 53 is not taught or suggested by the combination of the cited references.

(h) Claims 20, 22, 23, 24, 29-38, and 40-45 (argued separately)

Independent claim 20 is directed in part to a transdermal delivery system comprising an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, the system exhibiting the specific release profile (specific release rates at 24 hours, 48, hours, 72 hours, and 96 hours) and a plasma level of loratadine a steady state of about 3 ng/ml. Claim 20 further recites that the system maintains "a plasma level of loratadine of at least about 0.1 ng/ml by about 6 hours after application of said transdermal delivery system onto the skin of a human patient."

Appellants respectfully submit that a transdermal delivery system comprising an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, exhibiting the specific release profile (specific release rates at 24 hours, 48, hours, 72 hours, and 96 hours) and a plasma level of loratadine at steady state of about 3 ng/ml is not described or expected from the cited references, for the reasons given above with respect to claim 8.

Appellants further submit that the combination of the cited references does not teach or suggest a transdermal delivery system which maintains "a plasma level of loratadine of at least

about 0.1 ng/ml by about 6 hours after application of said transdermal delivery system onto the skin of a human patient" as recited in the instant claim 20, because there is no disclosure of any plasma levels of loratadine in the cited references.

Appellants therefore submit that a *prima facie* case of obviousness of claim 20 has not been established, and that claim 20 is not taught or suggested by the combination of the cited references.

Claims 22, 23, 24, 29-38, and 40-45 depend from claim 20, and therefore incorporate the features of claim 20 which are not taught or suggested by the combination of the cited references. Accordingly, a *prima facie* case of obviousness of claims 22, 23, 24, 29-38, and 40-45 has not been established.

(i) Claim 29 (argued separately)

Claim 29 recites a transdermal delivery system which maintains a plasma level of loratadine "from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval" of the transdermal delivery system.

The Examiner has not pointed out the portions of the cited references which describe such a system, nor were the Appellants able to find such a step in the cited references. As stated above, the cited references do not disclose any loratadine plasma levels.

Appellants therefore submit that a *prima facie* case of obviousness of claim 29 has not been established, and that claim 29 is not taught or suggested by the combination of the cited references.

(j) Claim 51 (argued separately)

Claim 51 is directed to a method of effectively treating seasonal allergic rhinitis, chronic

idiopathic urticaria, or both conditions in a human patient, transdermally, wherein the transdermal delivery system comprises loratadine and a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and a solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

The Examiner has not pointed out the portions of the cited references which would have suggested combining loratadine with (i) a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and (ii) a solvent selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate" as recited in claim 51. Appellants were not able to find such suggestion in the cited references.

Appellants therefore submit that a *prima facie* case of obviousness of claim 51 has not been established, and that claim 51 is not taught or suggested by the combination of the cited references.

(k) Claim 54 (argued separately)

Claim 54 is directed in part to a transdermal delivery system comprising "a solution of an active agent consisting of loratadine" as recited in claim 54.

Appellants submit that that the combination of the cited references does not teach or suggest a transdermal delivery system comprising "a solution of an active agent consisting of loratadine" as recited in claim 54, because the cited references do not teach or suggest a solution of loratadine. As stated above, the test for measuring the flux rates used in the Kogan reference is unsuitable for solution formulations, and the Reder reference cannot cure this deficiency of the Kogan reference, because there is no mention of loratadine in the Reder reference.

Accordingly, the combination of the cited references would not have suggested to one skilled in the art a transdermal delivery system comprising a solution of loratadine as recited in

claim 54.

Appellants therefore submit that a *prima facie* case of obviousness of claim 54 has not been established, and that claim 54 is not taught or suggested by the combination of the cited references.

(l) Claims 46, 49, 52 and 55

Independent claim 46 is directed in part to a **method** of treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient comprising the step of "maintaining a plasma level of loratadine at steady state of about 3 ng/ml" by administering loratadine transdermally to the human patient via a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof, the system exhibiting the claimed release profile (specific release rates at 24 hours, 48 hours, 72 hours, and 96 hours). Claim 46 recites that the transdermal delivery device used in the method comprises "a backing layer which is substantially impermeable to the loratadine or pharmaceutically acceptable salt thereof; and a reservoir layer consisting essentially of 20 to 90% by weight of a polymeric matrix, 0.1 to 30% by weight of a softening agent; 0.1 to 20% by weight of loratadine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% by weight of a solvent, for the loratadine or salt thereof."

Appellants respectfully submit that the Examiner has not pointed out the portion of the cited references which describes the composition recited in claim 46, nor were Appellants able to find such a portion in the cited references.

Appellants further submit that the combination of the cited references does not teach or suggest a step of "maintaining a plasma level of loratadine at steady state of about 3 ng/ml" and the release profile (specific release rates at 24 hours, 48 hours, 72 hours, and 96 hours), for the reasons given above with respect to claim 8.

Accordingly, Appellants submit that a *prima facie* case of obviousness of claim 46 has not been established, and claim 46 is not rendered obvious by the combination of the cited

references.

Claims 49, 52 and 55 depend from claim 46, and therefore incorporate features of claim 46 which are not taught or suggested by the combination of the cited references. Accordingly, a *prima facie* case of obviousness of claims 49, 52 and 55 has not been established.

(m) Claim 52 (argued separately)

Claim 52 is directed to a method of effectively treating seasonal allergic rhinitis, chronic idiopathic urticaria, or both conditions in a human patient, transdermally, wherein the transdermal delivery system comprises loratadine and a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

The Examiner has not pointed out the portions of the cited references which would have suggested to a skilled person to combine loratadine with (i) a softening agent selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and (ii) a solvent selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate" as recited in claim 52. Appellants were also not able to find such a suggestion in the cited references.

Appellants therefore submit that a *prima facie* case of obviousness of claim 52 has not been established, and that claim 52 is not taught or suggested by the combination of the cited references.

(n) Claim 55 (argued separately)

Claim 55 is directed in part to a method of effectively treating seasonal allergic rhinitis,

chronic idiopathic urticaria, or both conditions in a human patient, transdermally, wherein the transdermal delivery system comprise "a solution of an active agent consisting of loratadine" as recited in claim 55.

Appellants submit that that the combination of the cited references does not teach or suggest a transdermal delivery system comprising "a solution of an active agent consisting of loratadine" as recited in claim 55, because the cited references do not teach or suggest a solution of loratadine. As stated above, the test for measuring the flux rates used in the Kogan reference is unsuitable for solution formulations, and the Reder reference cannot cure this deficiency of the Kogan reference, because there is no mention of loratadine in the Reder reference.

Accordingly, the combination of the cited references would not have suggested to one skilled in the art a transdermal delivery system comprising a solution of loratadine as recited in claim 54.

Appellants therefore submit that a *prima facie* case of obviousness of claim 55 has not been established, and that claim 55 is not taught or suggested by the combination of the cited references.

B. THE STEADY STATE PLASMA CONCENTRATION OF LORATADINE SUGGESTED BY THE CITED REFERENCES IS DIFFERENT FROM THE STEADY STATE CONCENTRATION OF LORATADINE RECITED IN THE PRESENT CLAIMS, AND IS NOT EXPECTED FROM THE DISCLOSURE OF THE CITED REFERENCES.

Appellants submit that even if a *prima facie* case of obviousness has been established (a position which is vehemently denied), the present claims are patentable over the combination of the cited references, e.g., because Applicants have rebutted the *prima facie* case of obviousness by establishing that the steady state plasma concentration of loratadine suggested by the cited references is different from the steady state concentration of loratadine recited in instant independent claims 8, 20 and 46, and the steady state plasma concentration recited in the present independent claims is not expected from the cited references.

As stated above, instant independent claims 8, 20 and 46 all recite in part to a transdermal delivery system of loratadine which maintains "a plasma level or loratadine at steady state of about 3 ng/ml."

As stated above, the Reder reference does not mention loratadine and does not describe any devices comprising loratadine. The Reder reference therefore cannot provide any teaching with respect to the steady state plasma concentration of loratadine. The Kogan reference is therefore the only reference included in the present rejection which may have provided an indication or a suggestion of a steady state plasma loratadine concentration.

The steady state plasma concentration of loratadine purportedly suggested by the Kogan references is however different from the steady state concentration of loratadine recited in instant independent claims 8, 20 and 46. The Kogan reference describes the flux at the approximate plasma steady state of loratadine in Table I. The steady state plasma concentration from the devices of the Kogan reference may be calculated from the flux data in Table I of the Kogan reference by using the formulas described in the present specification.

The present specification describes two ways to calculate the dosing rate of loratadine (i.e., the amount of drug released per unit time from transdermal delivery system through the skin and into the bloodstream of a human patient). See paragraph [0123].

First, the specification states that the dosing rate is "a product of the steady state concentration of loratadine and a representative clearance rate." See paragraph [0123]. In other words, according to the present specification, dosing rate=C_{ss} x CL, where C_{ss} is loratadine's steady-state concentration, and CL is loratadine's clearance rate. The steady-steady concentration of loratadine may therefore be calculated by dividing the dosing rate of loratadine by its clearance rate. In other words, C_{ss}=dosing rate/CL.

The "flux" of the Final Gel of Table I of the Kogan reference (the highest flux listed in

Table I) is "2.26 mg/15 cm^2/day," or 94167 ng/hour (2.26/24x1000000=94167). The clearance rate of loratadine is 196000 ml/hr. See paragraph [0123]. The calculated steady state loratadine concentration after administration of the Final Gel of Kogan at approximately steady state is therefore 0.48 ng/ml (94167/196000=0.48). This calculated steady state concentration does not overlap with the steady state concentration of "about 3 ng/ml" recited in instant claim 8.

Similarly, calculating loratadine's steady state concentration after administration of the Final Gel of the Kogan reference by using the second formula described in the present specification does not overlap with the steady state concentration of "about 3 ng/ml" recited in the present claims. The present specification states that the dosing rate is equal to the "[t]he product of steady state concentration, volume of distribution and elimination rate constant." See paragraph [0123]. The elimination rate constant is "0.693/half-life." See Id. In other words, the dosing rate=C_{ss} x V_d x 0.693/half-life, where C_{ss} is loratadine's steady state plasma concentration and V_d is its volume of distribution. The steady-steady concentration of loratadine may be calculated by dividing the dosing rate by loratadine's volume of distribution and elimination rate constant. In other words, C_{ss}=dosing rate/(V_d x 0.693/half-life).

The dosing rate at approximate steady state after administration of the Final Gel of the Kogan reference is 2.26 mg/15cm^2/day, or 94167 ng/hour (2.26/24x1000000=94167). See Table I of the Kogan reference. According to the present specification, loratadine's V_d is 1660000 ml, and loratadine's half-life is 8.4 hours. See paragraph [0123]. The calculated steady state loratadine concentration after administration of the Final Gel at approximately steady state of the Kogan reference is therefore 0.69 ng/ml (94167/(1660000x0.693/8.4))=0.69).

This calculated steady state concentration of loratadine is in sharp contrast to the steady state concentration of "about 3 ng/ml" recited in independent claims 8, 20 and 46. Specifically, the steady state concentration of loratadine recited in the present claims is 4.3 times higher or 6.3 times higher than calculated the 0.69 ng/ml and 0.48 ng/ml steady state loratadine concentrations calculated from the flux data of the Kogan reference.

Appellants respectfully submit that the skilled person would understand that "about 3 ng/ml)" does not encompass values that are 4.3 times lower or 6.3 times lower than 3 ng/ml.

Accordingly, Appellants respectfully submit that "a plasma level of loratadine at steady state of about 3 ng/ml" is not expected from the devices of the cited references.

For the foregoing reasons, reversal of the rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the application is in condition for allowance. Favorable consideration of this Appeal Brief is respectfully requested.

Respectfully submitted,
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: _____
Oleg Ioselevich
(Reg. No. 56,963)

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 Seventh Avenue, 14th Floor
New York, NY 10018
Tel: (212) 736-1940
Fax: (212) 736-2427

APPENDIX A:

PENDING CLAIMS 18-11, 13, 14, 16, 20, 22-24, 29, 30, 32-38, and 40-55 OF U.S. APPLICATION SERIAL NO. 10/045,607.

Claim 8 (previously presented): A method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient, comprising administering loratadine transdermally to the human patient by applying a transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a softening agent; and (iv) a solvent, to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of the patient for at least 5 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval, said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml;

said transdermal delivery system having a mean relative release rate of from about 2.8 $\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours;

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours;

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 72 hours;

and a mean relative release rate of from about 1.8 $\mu g/cm^2/hr$ to about 9.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 9 (original): The method of claim 8 wherein the plasma level of loratadine at 48 hours does not decrease by more than 30% over the next 72 hours.

Claim 10 (original): The method of claim 8, further comprising maintaining an effective mean

relative release rate of said transdermal delivery system to provide a substantially first order plasma level increase of loratadine from the initiation of the dosing interval until about 48 to about 72 hours after the initiation of the dosing interval; and thereafter providing an effective mean relative release rate to provide a substantially zero order plasma level fluctuation of loratadine until the end of at least the five-day dosing interval.

Claim 11 (original): The method of claim 8, further comprising providing a mean relative release rate of loratadine from said transdermal delivery system to provide a plasma level of loratadine of at least about 0.1 ng/ml within about 6 hours after application of said transdermal delivery system onto the skin of the patient.

Claim 13 (original): The method of claim 8, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 14 (original): The method of claim 8, wherein said transdermal delivery system has a mean relative release rate from about 1.0 $\mu g/hour/cm^2$ to about 30.0 $\mu g/hour/cm^2$.

Claim 16 (previously presented): The method of claim 8, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63 $\mu g/cm^2$ to about 388 $\mu g/cm^2$ of the transdermal delivery system surface area at 24 hours; from about 105 $\mu g/cm^2$ to about 660 $\mu g/cm^2$ of the transdermal delivery system surface area at 48 hours; and from about 139 $\mu g/cm^2$ to about 854 $\mu g/cm^2$ of the transdermal delivery system surface area at 72 hours; and from about 162 $\mu g/cm^2$ to about 955 $\mu g/cm^2$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 20 (previously presented): A transdermal delivery system comprising (i) an active agent consisting of loratadine or a pharmaceutically acceptable salt thereof, (ii) a polymer, (iii) a

softening agent; and (iv) a solvent,

the transdermal delivery system provides a mean relative release rate of from about 2.8 $\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours;

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours;

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 72 hours; and

from about 1.8 $\mu g/cm^2/hr$ to about 9.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell having a receptor chamber containing a 40:60 mixture of ethanol:water; said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within 36 hours from the initiation of the dosing interval, and a plasma level of loratadine of at least about 0.1 ng/ml by about 6 hours after application of said transdermal delivery system onto the skin of a human patient; said transdermal delivery system maintaining a therapeutic blood level until the end of at least a five-day dosing interval and a plasma level of loratadine at steady state of about 3 ng/ml.

Claim 22 (previously presented): The transdermal delivery system of claim 20, which provides an in-vitro cumulative amount of permeation of from about 63 $\mu g/cm^2$ to about 388 $\mu g/cm^2$ of the transdermal delivery system surface area at 24 hours; from about 105 $\mu g/cm^2$ to about 660 $\mu g/cm^2$ of the transdermal delivery system surface area at 48 hours; and from about 139 $\mu g/cm^2$ to about 854 $\mu g/cm^2$ of the transdermal delivery system surface area at 72 hours, as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 23 (original): The transdermal delivery system of claim 20, comprising a backing layer which is impermeable to the active substance, a pressure-sensitive adhesive reservoir layer, and optionally a removable protective layer, the reservoir layer by weight comprising 20 to 90% of a polymeric matrix, 0.1 to 30% of a softening agent, 0.1 to 20% of loratadine base or of a

pharmaceutically acceptable salt thereof and 0.1 to 30% of a solvent for the loratadine or salt thereof.

Claim 24 (original): The transdermal delivery system of claim 20, which is a laminated composite comprising (a) a polymer backing layer that is substantially impermeable to loratadine or the pharmaceutically acceptable salt thereof; and (b) a reservoir layer comprising an acrylate or silicone based pressure-sensitive adhesive, 0.1 to 20% of loratadine base or of a pharmaceutically acceptable salt thereof, 0.1 to 30% of an ester of a carboxylic acid acting as a softening agent and 0.1 to 30% of a solvent for loratadine having at least one acidic group.

Claim 29 (previously presented): The transdermal delivery system of claim 20, wherein said therapeutic plasma level is maintained from about 0.1 ng/ml to about 3.3 ng/ml during the dosing interval for said transdermal delivery system.

Claim 30 (previously presented): The transdermal delivery system of claim 20, wherein said transdermal delivery system has a mean relative release rate from about 1.0 $\mu g/hour/cm^2$ to about 30.0 $\mu g/hour/cm^2$ of the transdermal delivery system surface area.

Claim 32 (previously presented): The transdermal delivery system of claim 20, wherein said transdermal delivery system provides an in-vitro cumulative amount of permeation of from about 63 $\mu g/cm^2$ to about 388 $\mu g/cm^2$ of the transdermal delivery system surface area at 24 hours; from about 105 $\mu g/cm^2$ to about 660 $\mu g/cm^2$ of the transdermal delivery system surface area at 48 hours; and from about 139 $\mu g/cm^2$ to about 854 $\mu g/cm^2$ of the transdermal delivery system surface area at 72 hours; and from about 162 $\mu g/cm^2$ to about 955 $\mu g/cm^2$ of the transdermal delivery system surface area at 96 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin and said cell has a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 33 (original): The transdermal delivery system according to claim 23, wherein the backing layer is composed of a flexible material.

Claim 34 (original): The transdermal delivery system according to claim 23, wherein the backing layer is selected from the group consisting of a flexible material, an inflexible material, and an aluminum foil.

Claim 35 (previously presented): The transdermal delivery system according to claim 23, wherein the polymeric matrix is at least one of rubber, a synthetic homo-, co- or blockpolymer, a urethane and silicone.

Claim 36 (original): The transdermal delivery system according to claim 23, wherein the softening agent is at least one of dodecanol, undecanol, octanol, a glycol and glycanol.

Claim 37 (original): The transdermal delivery system according to claim 23, wherein the solvent is a monoester of a dicarboxylic acid.

Claim 38 (original): The transdermal delivery system according to claim 23, wherein the solvent is at least one of monomethyl glutarate and monomethyl adipate.

Claim 40 (original): The transdermal delivery system according to claim 23, wherein by weight the polymer is present in about 55%, the loratadine in about 10%, the solvent in about 10% and the softener in about 15%.

Claim 41 (original): A transdermal delivery system according to claim 23, wherein the solvent is present in from about 25 to 100% the weight of the loratadine.

Claim 42 (original): The transdermal delivery system according to claim 23, which also comprises a removable protective layer.

Claim 43 (original): The transdermal delivery system according to claim 23, wherein the pressure-sensitive adhesive reservoir layer comprises a polymer based on an acrylate, a

methacrylate, a silicone compound or a combination thereof.

Claim 44 (previously presented): The transdermal delivery system according to claim 23, wherein the softening agent is a medium-chain triglyceride of the caprylic/capric acids of coconut oil.

Claim 45 (original): The transdermal delivery system according to claim 23, wherein the solvent has at least one acidic group.

Claim 46 (previously presented): A method of effectively treating seasonal allergic rhinitus, chronic idiopathic urticaria, or both conditions in a human patient, comprising administering loratadine transdermally to the human patient by applying a transdermal delivery system containing loratadine or a pharmaceutically acceptable salt thereof to the skin of a patient, and maintaining said transdermal delivery system in contact with the skin of the patient for at least 5 days, said transdermal delivery system maintaining an effective mean relative release rate to provide a therapeutic blood level of said loratadine within three days from the initiation of the dosing interval, and thereafter maintaining a therapeutic blood level until the end of at least the five-day dosing interval, said transdermal delivery device maintaining a plasma level of loratadine at steady state of about 3 ng/ml;

said transdermal delivery device comprising a backing layer which is substantially impermeable to the loratadine or pharmaceutically acceptable salt thereof; and a reservoir layer consisting essentially of 20 to 90% by weight of a polymeric matrix, 0.1 to 30% by weight of a softening agent; 0.1 to 20% by weight of loratadine base or of a pharmaceutically acceptable salt thereof and 0.1 to 30% by weight of a solvent, for the loratadine or salt thereof;

said transdermal delivery system having a mean relative release rate of from about 2.8 $\mu g/cm^2/hr$ to about 16.2 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 24 hours;

from about 2.3 $\mu g/cm^2/hr$ to about 13.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 48 hours;

from about 2.0 $\mu g/cm^2/hr$ to about 11.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 72 hours;

and a mean relative release rate of from about 1.8 $\mu g/cm^2/hr$ to about 9.9 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 96 hours ; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 47 (previously presented): The method of claim 8, wherein said transdermal delivery system has a mean relative release rate of from about 1.5 $\mu g/cm^2/hr$ to about 8.5 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 120 hours;

from about 2.4 $\mu g/cm^2/hr$ to about 7.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 144 hours;

and from about 1.5 $\mu g/cm^2/hr$ to about 6.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 48 (previously presented): The transdermal delivery system of claim 20, wherein said transdermal delivery system has a mean relative release rate of from about 1.5 $\mu g/cm^2/hr$ to about 8.5 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 120 hours;

from about 2.4 $\mu g/cm^2/hr$ to about 7.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 144 hours;

and from about 1.5 $\mu g/cm^2/hr$ to about 6.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 49 (previously presented): The method of claim 46, wherein said transdermal delivery system has a mean relative release rate of from about 1.5 $\mu g/cm^2/hr$ to about 8.5 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 120 hours;

from about 2.4 $\mu g/cm^2/hr$ to about 7.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 144 hours;

and from about 1.5 $\mu g/cm^2/hr$ to about 6.7 $\mu g/cm^2/hr$ of the transdermal delivery system surface area at 168 hours; as determined via an in-vitro permeation test utilizing a Valia-Chien cell where the membrane is a human cadaver skin, said cell having a receptor chamber containing a 40:60 mixture of ethanol:water.

Claim 50 (previously presented): The method of claim 8, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 51 (previously presented): The transdermal delivery system of claim 20, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 52 (previously presented): The method of claim 46, wherein a softening agent is selected from the group consisting of dodecanol, undecanol, octanol, a glycol, glycanol and a medium-chain triglyceride of the caprylic/capric acids of coconut oil; and the solvent is selected from the group consisting of a monoester of a dicarboxylic acid, monomethyl glutarate and monomethyl adipate.

Claim 53 (previously presented): The method of claim 8, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.

Claim 54 (previously presented): The transdermal delivery system of claim 20, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.

Claim 55 (previously presented): The method of claim 46, wherein the transdermal delivery system comprises a solution of the loratadine or a pharmaceutically acceptable salt thereof.

APPENDIX B

Evidence Appendix under 37 C.F.R. § 41.37(c)(ix):

No evidence pursuant to 37 C.F.R. §§ 1.130, 1.131 or 1.132 and relied upon in the appeal has been submitted by appellants or entered by the examiner.

APPENDIX C

Related proceedings Appendix under 37 C.F.R. § 41.37(c)(x):

As stated in "2. RELATED APPEALS AND INTERFERENCES" of this appeal brief, appellants, their legal representatives, and assignee are not aware of any appeal or interference that directly affects, will be directly affected by, or will have a bearing on the Board's decision in this appeal.